



## Clinical trial results:

### A Randomised, Double-blind, Placebo-controlled Parallel Group Study to Assess the Efficacy and Safety of Induction Therapy with LYC-30937-EC in Subjects with Active Ulcerative Colitis

#### Summary

EudraCT number	2016-000518-31
Trial protocol	NL HU PL CZ
Global end of trial date	26 March 2018

#### Results information

Result version number	v1 (current)
This version publication date	01 April 2020
First version publication date	01 April 2020

#### Trial information

##### Trial identification

Sponsor protocol code	LYC-30937-2001
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02762500
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	Lycera Corp.
Sponsor organisation address	620 West Germantown Pike, Suite 400, Plymouth Meeting, United States, PA 19462
Public contact	Lycera Clinical Department, Lycera Corp., 001 6104575095, 30937_Clinical_Operations@Lycera.com
Scientific contact	Lycera Clinical Department, Lycera Corp., 001 6104575095, 30937_Clinical_Operations@Lycera.com

Notes:

##### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 October 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	26 March 2018
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to assess the efficacy of LYC-30937-EC in inducing remission compared with placebo in subjects with active ulcerative colitis over a treatment duration of 8 weeks.

Protection of trial subjects:

The study was performed in accordance with the protocol, International Council for Harmonisation good clinical practice guidelines, and applicable local regulatory requirements and laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Poland: 81
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	United States: 28
Country: Number of subjects enrolled	Serbia: 5
Worldwide total number of subjects	124
EEA total number of subjects	91

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	117

From 65 to 84 years	7
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled at 42 study centers within the United States, Poland, Hungary, Czech Republic, Serbia and Netherlands. Study centers included academic medical centers and non-academic medical clinics.

### Pre-assignment

Screening details:

The screening visit took place up to 28 days (4 weeks) prior to randomization and the participant's first dose of study drug. Screening occurred over multiple days to complete and obtain results for all assessments. Participants who meet all eligibility requirements returned for the next phase of the study.

### Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	LYC-30937-EC 25 mg

Arm description:

LYC-30937-EC was administered orally, once daily from Day 1 through the end of the double-blind treatment phase (Visit 6/Week 8) for a total of 57 days of treatment.

Arm type	Experimental
Investigational medicinal product name	LYC-30937-EC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Modified-release capsule, soft
Routes of administration	Oral use

Dosage and administration details:

LYC-30937-EC 25 mg was administered once daily as a single delayed release, enteric coated hydroxyl-propyl-methyl-cellulose (HPMC) capsule. Administration occurred in the morning upon awaking after fasting overnight. Participants should not have eaten for approximately 1 hour (or more) after taking study drug, except for the randomisation visit where participants were dosed in the clinic at least 2 hours after their morning meal.

<b>Arm title</b>	Placebo
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Arm description:

Placebo was administered orally, once daily from Day 1 through the end of the double-blind treatment phase (Visit 6/Week 8) for a total of 57 days of treatment.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Modified-release capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Matching placebo for LYC-30937-EC was administered once daily as a single, delayed release, enteric coated HPMC capsule. Administration occurred in the morning upon awaking after fasting overnight. Participants should not have eaten for approximately 1 hour (or more) after taking study drug, except for the randomisation visit where participants were dosed in the clinic at least 2 hours after their morning meal.

<b>Number of subjects in period 1</b>	LYC-30937-EC 25 mg	Placebo
Started	62	62
Completed	60	59
Not completed	2	3
Consent withdrawn by subject	1	1
Adverse event, non-fatal	-	2
Lack of efficacy	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	LYC-30937-EC 25 mg
Reporting group description: LYC-30937-EC was administered orally, once daily from Day 1 through the end of the double-blind treatment phase (Visit 6/Week 8) for a total of 57 days of treatment.	
Reporting group title	Placebo
Reporting group description: Placebo was administered orally, once daily from Day 1 through the end of the double-blind treatment phase (Visit 6/Week 8) for a total of 57 days of treatment.	

Reporting group values	LYC-30937-EC 25 mg	Placebo	Total
Number of subjects	62	62	124
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	43.8 ± 11.94	39.3 ± 13.26	-
Gender categorical Units: Subjects			
Female	27	25	52
Male	35	37	72
Baseline Total Mayo Score (TMS)			
TMS range: 0 (normal/no disease) to 12 (severe disease). TMS comprised 4 subscores: stool frequency subscore, rectal bleeding subscore, endoscopy findings subscore, and physician's global assessment subscore. One participant in the placebo treatment arm did not have a complete Mayo score at baseline and therefore they were not included in this analysis population.			
Units: Units on a scale arithmetic mean standard deviation	7.9 ± 1.46	7.8 ± 1.77	-
Baseline Modified Mayo Score (MMS)			
MMS range: 0 (normal/no disease) to 9 (severe disease). MMS comprised 3 subscores: stool frequency subscore, rectal bleeding subscore, and endoscopy findings subscore. One participant in the placebo treatment arm did not have a complete Mayo score at baseline and therefore they were not included in this analysis population.			
Units: Units on a scale arithmetic mean standard deviation	6.0 ± 1.38	5.7 ± 1.55	-

## End points

### End points reporting groups

Reporting group title	LYC-30937-EC 25 mg
Reporting group description: LYC-30937-EC was administered orally, once daily from Day 1 through the end of the double-blind treatment phase (Visit 6/Week 8) for a total of 57 days of treatment.	
Reporting group title	Placebo
Reporting group description: Placebo was administered orally, once daily from Day 1 through the end of the double-blind treatment phase (Visit 6/Week 8) for a total of 57 days of treatment.	

### Primary: Number of Participants Achieving Clinical Remission at Week 8 Using the MMS

End point title	Number of Participants Achieving Clinical Remission at Week 8 Using the MMS
End point description: The MMS is a tool designed to measure disease activity for ulcerative colitis. Scoring ranges from 0 to 9 points and consists of 3 subscores (stool frequency, rectal bleeding, and endoscopy findings), each graded 0 to 3 with higher score indicating more severe disease activity. Endoscopy findings scoring was performed centrally. Clinical remission was defined as a Mayo stool frequency subscore of less than or equal to ( $\leq 1$ ), Mayo rectal bleeding subscore of 0 and a Mayo endoscopy findings subscore of $\leq 1$ .	
End point type	Primary
End point timeframe: 8 weeks	

End point values	LYC-30937-EC 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: Number of participants	7	12		

### Statistical analyses

Statistical analysis title	Response Rate Difference
Statistical analysis description: The difference in the proportion of participants who achieved a clinical remission at Week 8 of treatment (LYC-30937-EC minus placebo) and corresponding 90% confidence interval were estimated. Participants who were missing the Week 8 MMS assessment were assumed to have not achieved clinical remission.	
Comparison groups	LYC-30937-EC 25 mg v Placebo

Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority <sup>[1]</sup>
P-value	= 0.106
Method	1-sided Pearson chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-8.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-18.6
upper limit	2.5

Notes:

[1] - Statistical comparisons between the LYC-30937-EC treatment arm and placebo were done using a 1-sided Pearson chi-square test at the 5% level of significance ( $\alpha = 0.05$ ).

## Secondary: Number of Participants Achieving Clinical Remission at Week 8 Using the TMS

End point title	Number of Participants Achieving Clinical Remission at Week 8 Using the TMS
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End point description:

The TMS is a tool designed to measure disease activity for ulcerative colitis. Scoring ranges from 0 to 12 points and consists of 4 subscores (stool frequency, rectal bleeding, endoscopy findings, and physicians global assessment), each graded 0 to 3 with higher score indicating more severe disease activity. Endoscopy findings scoring was performed centrally. Clinical remission was defined as a TMS of  $\leq 2$ , with no individual subscore greater than ( $>$ ) 1 and rectal bleeding score of 0.

End point type	Secondary
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End point timeframe:

8 weeks

End point values	LYC-30937-EC 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: Number of participants	7	12		

## Statistical analyses

Statistical analysis title	Response Rate Difference
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Statistical analysis description:

The difference in the proportion of participants who achieved a clinical remission at Week 8 of treatment (LYC-30937-EC minus placebo) and corresponding 90% confidence interval were estimated. Participants who were missing the Week 8 TMS assessment were assumed to have not achieved clinical remission.

Comparison groups	LYC-30937-EC 25 mg v Placebo
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Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority <sup>[2]</sup>
P-value	= 0.106
Method	1-sided Pearson chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-8.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-18.6
upper limit	2.5

Notes:

[2] - Statistical comparisons between the LYC-30937-EC treatment arm and placebo were done using a 1-sided Pearson chi-square test at the 5% level of significance ( $\alpha = 0.05$ ).

## Secondary: Number of Participants with a Clinical Response at Week 8 Using the MMS

End point title	Number of Participants with a Clinical Response at Week 8 Using the MMS
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End point description:

The MMS is a tool designed to measure disease activity for ulcerative colitis. Scoring ranges from 0 to 9 points and consists of 3 subscores (stool frequency, rectal bleeding, and endoscopy findings), each graded 0 to 3 with higher score indicating more severe disease activity. Endoscopy findings scoring was performed centrally. Clinical response was defined as a reduction from the baseline MMS of greater than or equal to ( $\geq$ ) 2 points and  $\geq 25\%$ , and a decrease from baseline in rectal bleeding score of  $\geq 1$  point or an absolute rectal bleeding score of  $\leq 1$  point.

End point type	Secondary
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End point timeframe:

8 weeks

End point values	LYC-30937-EC 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: Number of participants	32	36		

## Statistical analyses

Statistical analysis title	Response Rate Difference
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Statistical analysis description:

The difference in the proportion of participants who achieved a clinical response at Week 8 of treatment (LYC-30937-EC minus placebo) and corresponding 90% confidence interval were estimated. Participants who were missing the Week 8 MMS assessment were assumed to have not achieved clinical response.

Comparison groups	LYC-30937-EC 25 mg v Placebo
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Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority <sup>[3]</sup>
P-value	= 0.235
Method	1-sided Pearson chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-6.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	-21.1
upper limit	8.2

Notes:

[3] - Statistical comparisons between the LYC-30937-EC treatment arm and placebo were done using a 1-sided Pearson chi-square test at the 5% level of significance( $\alpha = 0.05$ ).

## Secondary: Number of Participants with a Clinical Response at Week 8 Using the TMS

End point title	Number of Participants with a Clinical Response at Week 8 Using the TMS
End point description:	
<p>The TMS is a tool designed to measure disease activity for ulcerative colitis. Scoring ranges from 0 to 12 points and consists of 4 subscores (stool frequency, rectal bleeding, endoscopy findings, and physicians global assessment), each graded 0 to 3 with higher score indicating more severe disease activity. Endoscopy findings scoring was performed centrally. Clinical response was defined as a reduction from baseline TMS of <math>\geq 3</math> points and <math>\geq 30\%</math>, and a decrease from baseline in rectal bleeding score of <math>\geq 1</math> point or an absolute rectal bleeding score of <math>\leq 1</math> point.</p>	
End point type	Secondary
End point timeframe:	
8 weeks	

End point values	LYC-30937-EC 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: Number of participants	26	32		

## Statistical analyses

Statistical analysis title	Response Rate Difference
Statistical analysis description:	
<p>The difference in the proportion of participants who achieved a clinical response at Week 8 of treatment (LYC-30937-EC minus placebo) and corresponding 90% confidence interval were estimated. Participants who were missing the Week 8 TMS assessment were assumed to have not achieved clinical response.</p>	
Comparison groups	LYC-30937-EC 25 mg v Placebo

Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority <sup>[4]</sup>
P-value	= 0.14
Method	1-sided Pearson chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-9.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	-24.3
upper limit	5

Notes:

[4] - Statistical comparisons between the LYC-30937-EC treatment arm and placebo were done using a 1-sided Pearson chi-square test at the 5% level of significance( $\alpha = 0.05$ ).

## Secondary: Absolute Change From Baseline in TMS at Week 8

End point title	Absolute Change From Baseline in TMS at Week 8
End point description:	
The TMS is a tool designed to measure disease activity for ulcerative colitis. Scoring ranges from 0 to 12 points and consists of 4 subscores (stool frequency, rectal bleeding, endoscopy findings, and physicians global assessment), each graded 0 to 3 with higher score indicating more severe disease activity. Endoscopy findings scoring was performed centrally. A decrease from baseline to Week 8 in the TMS indicates a reduction in disease activity.	
End point type	Secondary
End point timeframe:	
Baseline to Week 8	

End point values	LYC-30937-EC 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59 <sup>[5]</sup>	58 <sup>[6]</sup>		
Units: Change from baseline				
least squares mean (standard error)	-2.49 ( $\pm$ 0.33)	-2.67 ( $\pm$ 0.33)		

Notes:

[5] - Number of participants with non-missing change from baseline in TMS

[6] - Number of participants with non-missing change from baseline in TMS

## Statistical analyses

Statistical analysis title	Statistical Analysis of Change from Baseline TMS
Statistical analysis description:	
Participants who were missing the baseline or Week 8 TMS were excluded from the analysis.	
Comparison groups	LYC-30937-EC 25 mg v Placebo
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority <sup>[7]</sup>
P-value	= 0.708
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.18

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.6
upper limit	0.95

Notes:

[7] - The mean change from baseline at Week 8 was evaluated using an analysis of covariance (ANCOVA) with a factor for treatment and a covariate for baseline TMS.

### Secondary: Percent Change From Baseline to Week 8 in Fecal Calprotectin in Participants with Baseline Fecal Calprotectin $\geq$ 250 micrograms per gram ( $\mu\text{g/g}$ )

End point title	Percent Change From Baseline to Week 8 in Fecal Calprotectin in Participants with Baseline Fecal Calprotectin $\geq$ 250 micrograms per gram ( $\mu\text{g/g}$ )
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End point description:

Fecal calprotectin is an inflammatory marker for the gastrointestinal tract and considered as a measurement of neutrophil migration to the gastrointestinal tract. Higher values indicate more serious inflammation. A decrease from baseline to Week 8 in fecal calprotectin indicates a reduction in inflammation. Only participants with a baseline fecal calprotectin value  $\geq$  250  $\mu\text{g/g}$  were included.

End point type	Secondary
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End point timeframe:

Baseline to Week 8

End point values	LYC-30937-EC 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44 <sup>[8]</sup>	37 <sup>[9]</sup>		
Units: Percent change from baseline				
least squares mean (standard error)	-35.22 ( $\pm$ 13.81)	9.37 ( $\pm$ 15.07)		

Notes:

[8] - Participants with non-missing percent change from baseline in fecal calprotectin

[9] - Participants with non-missing percent change from baseline in fecal calprotectin

### Statistical analyses

Statistical analysis title	Statistical Analysis of Fecal Calprotectin
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Statistical analysis description:

Participants who were missing the baseline or Week 8 fecal calprotectin were excluded from the analysis.

Comparison groups	LYC-30937-EC 25 mg v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority <sup>[10]</sup>
P-value	= 0.032
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-44.59

Confidence interval	
level	90 %
sides	2-sided
lower limit	-78.66
upper limit	-10.53

Notes:

[10] - The mean change from baseline at Week 8 was evaluated using an ANCOVA with a factor for treatment and a covariate for baseline fecal calprotectin.

### Other pre-specified: Number of Participants with Treatment Emergent Adverse Events (TEAEs), Serious TEAEs and TEAEs Leading to Discontinuation from the Study

End point title	Number of Participants with Treatment Emergent Adverse Events (TEAEs), Serious TEAEs and TEAEs Leading to Discontinuation from the Study
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End point description:

Adverse events (AEs) were collected from the time a participant signed the informed consent. TEAEs were AEs occurring or worsening after the first dose of study drug (LYC-30937-EC 25 mg or placebo). Severity of AEs was assessed by the Investigator using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03, with grading as follows: Grade 1 = mild (asymptomatic or mild symptoms), Grade 2 = moderate (minimal, local intervention, or noninvasive intervention indicated); Grade 3 = severe (or medically significant but not life-threatening); Grade 4 = life-threatening; Grade 5 = death.

End point type	Other pre-specified
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End point timeframe:

10 weeks

End point values	LYC-30937-EC 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: Number of participants				
Participants with $\geq 1$ TEAE	22	27		
Participants with $\geq 1$ serious TEAE	1	3		
Participants with TEAE leading to discontinuation	0	2		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs and serious AEs were collected from the time the participant signed informed consent through last participant visit (up to 14 weeks in total).

Adverse event reporting additional description:

All directly observed and spontaneously reported AEs were recorded. Participants were also questioned about AEs. Severity of AEs was graded according to NCI CTCAE v4.03. AEs not included in the NCI CTCAE lists were graded according to the NCI CTCAE general guidelines.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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### Reporting groups

Reporting group title	LYC-30937-EC 25 mg
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Reporting group description:

LYC-30937-EC was administered orally, once daily from Day 1 through the end of the double-blind treatment phase (Visit 6/Week 8) for a total of 57 days of treatment.

'Subjects affected by non-serious adverse events' is the number of participants affected by non-serious AEs occurring at >5%.

Reporting group title	Placebo
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Reporting group description:

Placebo was administered orally, once daily from Day 1 through the end of the double-blind treatment phase (Visit 6/Week 8) for a total of 57 days of treatment.

'Subjects affected by non-serious adverse events' is the number of participants affected by non-serious AEs occurring at >5%.

Serious adverse events	LYC-30937-EC 25 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 62 (3.23%)	3 / 62 (4.84%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 62 (1.61%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Sciatica			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 62 (1.61%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Clostridium difficile infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	LYC-30937-EC 25 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 62 (16.13%)	11 / 62 (17.74%)	
Nervous system disorders			
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 62 (9.68%)	5 / 62 (8.06%)	
occurrences (all)	6	6	
Gastrointestinal disorders			

Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 62 (6.45%)	6 / 62 (9.68%)	
occurrences (all)	4	8	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 May 2016	<p>The following changes were made:</p> <ul style="list-style-type: none"><li>• Section 6.5.7 (Monitoring Subjects for AEs of Special Interest) and Section 7.12 (Stopping Rules) were revised, and Section 7.12.1 (Suspension of Study) was added to be consistent with the Food and Drug Administration (FDA) industry guidance on drug-induced liver injury.</li><li>• The liver function test exclusion was reduced to 1.5 x the upper limit of normal.</li><li>• The new Lycera facsimile number was added to the cover page.</li><li>• Minor revisions/clarifications were made throughout.</li></ul>
22 June 2016	<p>The following changes were made:</p> <ul style="list-style-type: none"><li>• Exploratory efficacy endpoint referencing "mucosal healing" changed throughout to "endoscopic improvement" as histologic evaluation of mucosa to validate healing was not performed.</li><li>• Secondary efficacy endpoint Week 8 TMS clinical remission definition revised to include rectal bleeding score of 0.</li><li>• Section 4.4.1: Inclusion criteria 4 revised to require women of childbearing potential to use 2 highly effective forms of birth control.</li><li>• Section 4.4.2: Elevated serum creatinine added to Exclusion criteria 6 to exclude patients with renal impairment.</li><li>• Section 6.4.1 definition of left-sided disease added to clarify which subjects could have flexible sigmoidoscopy at week 8 based on demarcation of inflammation observed in Screening colonoscopy.</li><li>• Section 6.4.1 clarified that endoscopy video recording was to be provided for central reading and central readers had study specific training, including that a Mayo endoscopic score of 0 or 1 could not include any degree of "friability" as this was inconsistent with remission.</li><li>• Section 6.4.1 clarified that stool frequency and rectal bleeding data for Mayo scoring was obtained from the diary completed by the subjects. Also clarified that average stool frequency and rectal bleeding score calculated from the individual 3 consecutive days was used for the Mayo score.</li><li>• Section 6.5.7 revised to state that study drug was to be withheld in subjects who exhibited any of the listed laboratory elevations in liver biochemical parameters and lactate.</li><li>• Section 7.5 revised to add SAE reporting information including time frame for reporting SAEs to US FDA.</li><li>• Section 6.6.1.2 clarified serial pharmacokinetic sub-study blood sample collection.</li><li>• Section 7.10: sponsor medical monitor name and contact information added.</li><li>• Section 7.12: individual stopping criteria added based on abnormal ECG findings of prolonged QT/QTc interval.</li><li>• Section 11.1 removed statement that subjects were identified</li></ul>

07 December 2016	<p>The following changes were made:</p> <ul style="list-style-type: none"> <li>• Throughout protocol: revised all references to “anti-tumour necrosis factor” therapy to state “biologic” therapy</li> <li>• Section 1.0 revised to add countries participating in study and the estimated last subject last visit;</li> <li>• Sections 1.0 - 2.5 updated and reorganized</li> <li>• Section 4.1 revised language related to open-label extension protocol</li> <li>• Section 4.4.1 Inclusion criteria #2 revised to add clarity to histological evaluation if done at Screening</li> <li>• Section 4.4.1 Inclusion criteria #4 revised to add clarity to effective birth control</li> <li>• Section 4.4.1 Inclusion criteria #5 revised to add clarity</li> <li>• Section 4.4.1 Inclusion criteria #6 revised to add clarity</li> <li>• Section 4.4.2 Exclusion criteria #3 revised for clarity regarding bleeding disorders</li> <li>• Section 4.4.2 Exclusion criteria #10 revised to define history of uveitis</li> <li>• Section 4.4.2 Exclusion criteria #12 revised to define type of colon polyp being referenced</li> <li>• Section 4.4.2 Exclusion criteria #19 revised to remove reference to use of “topical” 5-ASA and steroids</li> <li>• Section 5.5.2-5.5.3 revised to add clarity related to IWRS and compliance</li> <li>• Section 5.6 revised to be consistent with other sections of protocol and to specify that corticosteroid taper was not allowed during the study</li> <li>• Section 6.2.1 revised wording related to timing for Screening procedures when a subject was already scheduled for a colonoscopy</li> <li>• Section 6.5.4 revised to clarify calculation of QTcF will not be done by sites</li> <li>• Section 6.5.7 revised to specify that Baseline abdominal pain and vomiting was to be carefully assessed</li> <li>• Section 7.4 revised to include the CTCAE criteria for assessment of AE severity</li> <li>• Section 7.12.1 study suspension criteria revised to state that if 50% of subjects experienced clinically important drug-related AEs (instead of TESAEs) with severity of CTCAE Grade 2</li> <li>• Appendix B revised: hepatitis blood sample removed.</li> </ul>
05 June 2017	<p>The following changes were made:</p> <ul style="list-style-type: none"> <li>• Section 4.4.1 Inclusion criteria #5 revised to allow inclusion of subjects on concomitant thiopurine UC treatment and to allow subjects on no UC treatment.</li> <li>• Section 4.4.1 Inclusion criteria #6 revised to include thiopurine.</li> <li>• Section 4.4.2 Exclusion criteria #7 revised to remove reference to thiopurines and to reduce the washout of other immunomodulatory medications to 4 weeks prior to the Screening endoscopy.</li> <li>• Section 4.4.2 Exclusion criteria #10 removed (history of uveitis).</li> <li>• Section 4.4.2 Exclusion criteria #12 revised to allow subjects with a history of cancer that was in remission for <math>\geq 5</math> years and exclude subjects with cancer diagnosed within the past 5 years unless approved by the study medical monitor.</li> <li>• Section 4.4.2 Exclusion criteria #17 biologic washout period determination revised and Appendix D added.</li> <li>• Section 4.4.2 Exclusion criteria #19 revised to allow use of rectal 5-ASA medications.</li> <li>• Section 5.6 revised to allow concomitant use of a stable dose of thiopurines.</li> <li>• Section 6.2.6 revised to specify that the Visit 6 date was the date of study completion.</li> <li>• Section 6.6.1.1, Table 3 footnote and Appendix B revised to specify that up to 20 subjects were planned to participate in the safety PK sub-study.</li> <li>• Section 6.6.1.2, Table 3 footnote and Appendix B revised to specify that up to 12 subjects were planned to participate in the serial PK sub-study.</li> <li>• Section 7.12 revised to specify that a repeat ECG was to be performed if QT/QTc prolongation stopping criteria were noted for confirmation.</li> </ul>

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported